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LEADING ARTICLE

Use of Biologic Agents in Combination with Other Therapies for the Treatment of Psoriasis

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Abstract Psoriasis is a chronic inflammatory skin disorder, which is associated with a significant negative impact on a patient's quality of life. Traditional therapies for psoriasis are often not able to meet desired treatment goals, and high-dose and/or long-term use is associated with toxicities that can result in end-organ damage. An improved understanding of the involvement of cytokines in the etiology of psoriasis has led to the development of biologic agents targeting tumor necrosis factor (TNF)- α and interleukins (ILs)-12/23. While biologic agents have improved treatment outcomes, they are not effective in all individuals with psoriasis. The combination of biologic agents with traditional therapies may provide improved therapeutic options for patients who inadequately respond to a single drug or when efficacy may be increased with supplementation of another treatment. In addition, combination therapy may reduce safety concerns and cumulative toxicity, as lower doses of individual agents may be efficacious when used together. This article reviews the current evidence available on the efficacy and safety of combining biologic agents with systemic therapies (methotrexate, cyclosporine, or retinoids) or with phototherapy, and the combination of biologic agents themselves. Guidance is provided to help physicians identify situations and the characteristics of

patients who would benefit from combination therapy with a biologic agent. Finally, the potential clinical impact of biologic therapies in development (e.g., those targeting IL-17A, IL-17RA, or IL-23 alone) is analyzed.

Key Points

Accumulating evidence supports the administration of biologic therapies in combination with systemic agents or phototherapy.

Limited data exist on the co-administration of two biologics.

Emerging, highly selective biologics may demonstrate the required efficacy to be administered as monotherapy.

1 Introduction

Psoriasis is a chronic inflammatory skin disease, which affects approximately 3 % of the general population in the USA [1]. The most common form of the disease, plaque psoriasis, is characterized by the development of chronic erythematous plaques covered with silvery white scales, which most commonly appear on the elbows, knees, scalp, umbilicus, and lumbar regions [2]. Psoriasis has been associated with a significant negative impact on the patient's quality of life, due to the disfiguring effect of the skin lesions and, for some, the functional impairment resulting from joint pain [3]. Additionally, individuals with psoriasis are more susceptible to specific debilitating comorbidities, including cardiometabolic dysfunction, fatigue, and depression [4–6].

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The treatment strategy for psoriasis depends on a variety of factors (e.g., the medical history, tolerability of therapies and potential for side effects, and disease severity). Regarding disease severity, there is no commonly accepted definition of mild versus moderate-to-severe psoriasis [7]. Moreover, a patient may have mild disease on the basis of body surface area (BSA) involvement, but localization of lesions in vulnerable areas (e.g., the face, feet, hands, and/or genitals) may warrant systemic therapy. Some guidelines provide specific criteria to help evaluate the severity of a patient's psoriasis, but all recognize the importance of assessing both the physical and psychosocial burden when considering the best treatment approach [7–10].

The US National Psoriasis Foundation recommends that patients with BSA involvement $<5\%$ should be considered candidates for topical therapy, whereas those with $BSA \geq 5\%$ should be considered candidates for systemic therapy alone or in combination with phototherapy [9]. A “rule of tens” has also been proposed, whereby $BSA >10\%$, Psoriasis Area Severity Index (PASI) >10 , or Dermatology Life-Quality Index (DLQI) >10 identify patients with severe disease [10]. More recently, a European consensus meeting defined mild psoriasis as $BSA \leq 10\%$, $PASI \leq 10$, and $DLQI \leq 10$; and moderate-to-severe psoriasis warranting systemic therapy as BSA or $PASI >10$ and $DLQI >10$ [7]. The American Academy of Dermatology (AAD) guidelines present a treatment decision tree based on the presence or absence of psoriatic arthritis and categorization of psoriasis as “limited” or “extensive” disease, but specific definitions of these terms are not provided [8].

The ultimate goal of systemic therapy is to eliminate the systemic inflammatory burden of psoriasis and to completely clear the skin [7]. Historically, conventional systemic treatment options for psoriasis have included methotrexate, cyclosporine, and oral retinoids such as acitretin [11]. However, the use of these systemic agents has been limited by insufficient clinical efficacy, safety concerns, or both [7, 12, 13]. Cyclosporine is generally considered the most effective of these agents, providing a rapid response [14]. However, nephrotoxicity, hypertension, and numerous drug interactions may limit its use. Moreover, the duration of cyclosporine use is limited when it is prescribed for psoriasis (1 year in the USA, 2 years in the UK). The hepatotoxic effects of methotrexate necessitate particular caution when it is used in patients with liver problems or in those consuming large amounts of alcohol. Both methotrexate and retinoids are teratogenic [14].

None of these agents fully meets the needs of patients, and many are contraindicated because of the presence of comorbidities. Patient dissatisfaction with conventional systemic therapies has been well documented. Patients have voiced displeasure over inconvenient administration

of traditional psoriasis therapies and their related side effects (e.g., hirsutism with cyclosporine, gastrointestinal intolerance with methotrexate, and hair loss and cheilitis with acitretin) [13]. Approximately 40 % of patients on systemic therapy alone have expressed dissatisfaction with their treatment outcomes [15], and overall patient satisfaction has been found to be lower with systemic therapy (cyclosporine, methotrexate, or acitretin) than with biologic agents, biologic/methotrexate combinations, or phototherapy [16]. Dissatisfaction with therapy is a major contributor to diminished adherence among patients with dermatologic disorders; inadequate treatment can therefore add to the already substantial burden of poor health-related quality of life associated with psoriasis [17, 18].

Over the past two decades, our understanding of the etiology of psoriasis has evolved; it is now recognized that both the innate and adaptive immune pathways are involved in its pathogenesis [19, 20]. Consequently, drugs that target specific components of the immune responses involved in the pathogenesis of psoriasis have been developed in an attempt to improve treatment efficacy, safety, and tolerability [21]. These agents include biologics that target cytokines such as tumor necrosis factor (TNF)- α and interleukins (ILs) 12/23 [21]. Despite remarkable improvements in psoriasis treatment outcomes with biologic therapy, however, many patients still do not achieve the desired outcome (Table 1) [22–30], have a prolonged time to response, or fail to maintain efficacy improvements over time. Tolerability may also be an issue (e.g., infections with TNF- α antagonists).

Combination systemic therapy may optimize treatment outcomes because of the potential of additive or synergistic efficacy. In addition, the dose of individual agents may be reduced, thereby decreasing toxicity and improving tolerability and compliance [31]. Up to 30 % of patients receiving a TNF- α antagonist also receive concomitant treatment with a traditional systemic agent such as methotrexate [32, 33]. Data are more limited with other drug combinations, including combinations with biologic agents [21, 31, 34]. In this paper, we review the rationale for the use of combination therapy in the management of psoriasis, along with evidence identified through a nonsystematic review of the literature that is currently available to support this practice. We also discuss new developments in the treatment of psoriasis, which may lessen the need for combination therapy to achieve desired outcomes.

2 Rationale for Combination Therapy

Some of the rationales for combining conventional therapies with biologic agents for psoriasis treatment have a historical basis in the treatment of psoriatic arthritis. In

Table 1 Results from clinical trials on the efficacy of biologic therapies for the treatment of psoriasis [22–30]

	Etanercept		
	25 mg QW	25 mg BIW	50 mg BIW
Psoriasis Study I (672 patients)			
PASI 75 at week 12	14 %	32 %	47 %
Psoriasis Study II (611 patients)			
PASI 75 at week 12	–	32 %	46 %
	Ustekinumab (at weeks 0 and 4)		
	45 mg	90 mg	
PHOENIX I (766 patients)			
PASI 75 at week 12	67 %	66 %	
PHOENIX II (1,230 patients)			
PASI 75 at week 12	67 %	76 %	
	Infliximab (at weeks 0, 2, and 6)		
	3 mg/kg	5 mg/kg	
EXPRESS (378 patients)			
PASI 75 at week 10	–	80 %	
EXPRESS II (835 patients)			
PASI 75 at week 10	70 %	75 %	
SPIRIT (249 patients)			
PASI 75 at week 10	72 %	88 %	
			Adalimumab 40 mg EOW
Psoriasis Study I (1,212 patients)			
PASI 75 at week 16			71 %
Psoriasis Study II (147 patients)			
PASI 75 at week 16			78 %

BIW biweekly, EOW every other week, PASI 75 improvement in the Psoriasis Area Severity Index of ≥ 75 %, QW once weekly

particular, methotrexate has been widely used in combination with biologic agents in clinical trials involving patients with psoriatic arthritis [35–39]. Indeed, the AAD guidelines recommend disease-modifying antirheumatic drugs (e.g., methotrexate), TNF- α antagonists, or a combination of these agents for moderate to severely active psoriatic arthritis [40]. The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) recommends that “a combination of two or more agents could be used in those patients who fail to respond to a single agent, or who present (with) joint damage progression in spite of treatment” [41]. The European League Against Rheumatism (EULAR) has made similar recommendations, but notes that there is a lack of robust evidence in psoriatic arthritis for this type of therapy [42].

The basis for these recommendations is rooted in the potential benefits that combination therapy may offer these patients, and can be extended to patients with psoriasis. These rationales include the potential efficacy synergies that may permit a more complete response and achieve a response more quickly, or both, as well as a potentially diminished risk of specific safety concerns that are caused by broad immunosuppressive therapy or that have been otherwise associated with conventional therapies (e.g., hepatotoxicity, nephrotoxicity, and bone marrow toxicity) [21, 43]. In addition, because the increased cytokine levels associated with psoriasis may also be associated with other inflammatory comorbid conditions, interventions targeting these upregulated cytokines may also provide a broader benefit to the patient. For example, a recent literature review found that methotrexate and TNF- α inhibitors may reduce cardiovascular events in individuals with psoriasis, although additional studies are required in this area [44]. Additionally, data from clinical trials evaluating adalimumab in rheumatoid arthritis demonstrate that patients on methotrexate had significantly higher blood levels of adalimumab than patients treated with adalimumab alone [30]. Thus, methotrexate, through an unknown mechanism, may boost drug levels of adalimumab. It is important to note that exposure to multiple drugs could also increase the risk of certain side effects, depending on the safety profiles of the individual agents being combined.

Combination therapies that include biologic agents may be particularly appropriate for a number of specific groups of patients with psoriasis (Table 2) [45–48]. The AAD guidelines do not provide specific recommendations in this regard [49]. The recent European consensus guidelines recommend that combination therapy should be considered for individuals who are switching to a biologic agent and in whom it may be useful to taper the previous systemic therapy before discontinuation to prevent a disease flare [32, 45, 50]. Additionally, patients with complications or comorbidities may benefit from the use of combination therapy with biologics. Patients with specific safety or toxicity concerns, such as methotrexate-related hepatotoxicity or cyclosporine-related nephrotoxicity, may also benefit from combination therapy with a biologic agent [47]. Additionally, combination therapy may help in the prevention or treatment of adverse events in certain patients (e.g., use of retinoids in a patient at risk of non-melanoma skin cancer, or anti-TNF therapy in a patient with comorbid Crohn's disease) [45, 51, 52]. Patients who may benefit from less rigorous treatment regimens with lower doses may also be candidates for combination therapy [53, 54]. In addition, there may be certain situations in which it would be appropriate to initiate combination therapy, such as at times when flares consistently occur (e.g., in the winter) or when a patient changes insurance

Table 2 Potential indications for systemic combination therapies including biologic agents [45–48]

-
- Inadequate efficacy of monotherapies
 - Tolerability concerns
 - Complications or comorbidities (e.g., psoriatic arthritis, cardiovascular disease)
 - Bridging treatment in patients switching between systemic therapies
 - Potential for intermittent or continuous use during long-term treatment for relapsing disease
 - Tailoring therapy to meet individual patients' needs
-

and there are concerns about possible disruptions in therapy.

3 Clinical Experience with Combination Therapy

Although combination therapy with biologic agents has been widely used in the treatment of rheumatoid arthritis and psoriatic arthritis, only a few small-scale, randomized, controlled trials have been undertaken in patients with psoriasis [21, 31, 34, 48, 55]. In many cases, studies of combination therapy with biologic agents have been conducted against a background of treatment with conventional systemic therapies, such as methotrexate, in individuals without an adequate response to such treatment. Additionally, many of these studies were performed in patients with psoriatic arthritis; the effect of therapy on their psoriasis was also recorded as a secondary consideration [35–39]. Recently, the European consensus meeting developed recommendations for combining biologic and conventional systemic psoriasis therapies to provide some degree of structure for this practice; these recommendations are reported in Table 3 [50].

3.1 Combinations Involving Methotrexate

Initial findings of improved skin clearance in individuals with psoriatic arthritis after treatment with methotrexate and adalimumab led to further investigation of combined methotrexate and biologic therapy in psoriasis-specific populations [36]. In an open-label pilot study of 59 patients with active psoriasis (PASI ≥ 8 , BSA $> 10\%$, or both) without an adequate response to long-term (≥ 3 months) methotrexate therapy, patients were randomized to receive either etanercept and continued methotrexate or etanercept with methotrexate tapered and discontinued [56]. After 24 weeks, the proportion of patients with a Physicians' Global Assessment (PGA) rating of "clear" or "almost clear" was significantly higher in the combination therapy group than in the etanercept monotherapy group (66.7 versus 37.0 %, respectively; $P = 0.025$). The same trend was also observed in the improvement of PASI scores by at least 75 % (PASI 75) at weeks 12 and 24. The adverse event rates were 75.0 % in the monotherapy group and

61.3 % in the combination group; adverse infectious events were the most frequent (25.0 and 38.7 %, respectively) [56]. The recent comparison of efficacy between etanercept and etanercept in combination with methotrexate by Gottlieb et al. [57] is one of the most robust combination trials to date in patients with moderate-to-severe psoriasis. Almost 45 % of patients in this trial had received prior systemic therapy, including methotrexate in about 17 % of patients. In this randomized, double-blind trial of 478 patients (BSA $\geq 10\%$, PASI ≥ 10), PASI 75 response rates at 24 weeks were significantly higher with combination therapy than with etanercept alone (77.3 versus 60.3 %, respectively; $P < 0.0001$), as were other PASI response rates (Fig. 1) [57]. Combination therapy was also associated with a significant increase in the proportion of patients with a PGA rating of "clear" or "almost clear", compared with etanercept alone (week 12: 65.5 versus 47.0 %; week 24: 71.8 versus 54.3 %; both $P = 0.01$). Adverse events were reported in 74.9 % of patients receiving combination therapy and in 59.8 % of those receiving etanercept monotherapy; the adverse event profiles of the two treatments were similar and included nasopharyngitis (9.6 % with combination therapy versus 10.9 % with monotherapy), headache (9.2 versus 9.2 %), and upper respiratory tract infection (8.4 versus 5.0 %).

The combination of methotrexate and biologic agents also improves psoriasis in individuals without previous methotrexate therapy. The multicenter, randomized, open-label RESPOND trial ($N = 115$) evaluated the efficacy of methotrexate alone or in combination with infliximab in patients with psoriasis and psoriatic arthritis who had not previously received methotrexate [58]. The mean weekly dose of methotrexate was 15.4 mg in the monotherapy group and 14.6 mg in the combination group; the combination group received infliximab 5 mg/kg at weeks 0, 2, 6, and 14. The baseline PASI scores were relatively low compared with those in most psoriasis trials, with mean scores of approximately 11.6 in the monotherapy group and 8.3 in the combination group. Among patients with baseline PASI measurements of ≥ 2.5 , the PASI 75 response rate at 16 weeks (a secondary outcomes measure) was 97.1 % with combination therapy and 54.3 % with methotrexate alone ($P < 0.0001$). Treatment-related adverse events occurred in 46 % of patients in the combination

Table 3 Recommendations for combining biologic therapies with conventional systemic therapy in patients with moderate-to-severe plaque psoriasis*Efficacy and safety of combination therapy*

1. There is no approved indication for any combination of a biologic agent with conventional systemic therapies in psoriasis
2. A conventional systemic therapy can be added to biologic monotherapy with the intention to improve efficacy, optimize the risk–benefit profile, reduce the risk of immunogenicity (with methotrexate), and enhance long-term disease management
3. For TNF antagonists, combination with methotrexate (5–15 mg/week) is safe and increases the long-term efficacy of the treatment regimen
4. Because of the lack of evidence and the potentially increased toxicity (e.g., an increased skin cancer risk), the combination of TNF antagonists or ustekinumab with cyclosporine should be used with caution
5. The combination of etanercept 25 mg/week with acitretin showed efficacy similar to that of 2×25 mg/week etanercept monotherapy. The combination of acitretin with lower doses of etanercept 25 mg/week has a safety profile comparable to that of monotherapy
6. The combination of adalimumab with acitretin may be considered
7. A treatment combination of methotrexate with ustekinumab may be used, but there are limited data on safety and efficacy
8. Data on the combination of acitretin with infliximab or ustekinumab are not currently available, but an increased clinical response might also be expected

Optimal safety monitoring of combination therapy

1. The optimal safety monitoring for combination therapy has not been determined
2. All parameters recommended to be monitored for each drug as monotherapy should be assessed
3. As a practical guide, the monitoring interval should be defined by the drug with the most stringent monitoring criteria
4. If synergistic toxicity is suspected, monitoring intervals may need to be reduced and additional parameters may need to be added

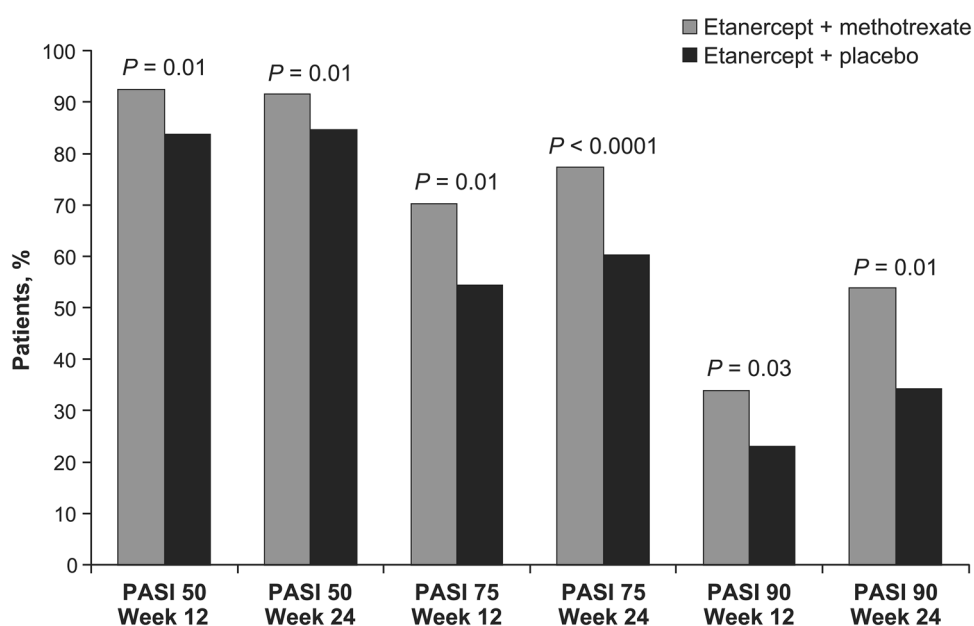
Patients with no response or insufficient response to combination therapy

1. The combination of a biologic with a conventional systemic therapy is an option in the treatment of psoriasis; however, there is no clinical trial evidence on which to provide answers to these questions
2. Conventional systemic therapy with methotrexate or acitretin can be added to a biologic monotherapy with the intention to improve efficacy, optimize the risk–benefit profile, reduce the risk of immunogenicity (with methotrexate), and enhance long-term disease management. The conventional systemic therapy should be added beginning with the lowest recommended dosage (e.g., 5–10 mg/week for methotrexate). The combined use of cyclosporine and a biologic raises safety concerns
3. If an adequate response is still not achieved:
 - Optimize the current therapy (e.g., increase the dosage of the conventional systemic therapy; increase the dose or decrease the treatment interval of the biologic)
 - Consider switching to another biologic drug

Adapted from Mrowietz et al. [50], with permission. © 2013 The Authors. Journal of the European Academy of Dermatology and Venereology © 2013 European Academy of Dermatology and Venereology

TNF tumor necrosis factor

Fig. 1 Proportions of patients with moderate-to-severe plaque psoriasis showing improvements in the Psoriasis Area Severity Index of ≥ 50 % (PASI 50), ≥ 75 % (PASI 75), and ≥ 90 % (PASI 90) at 12 and 24 weeks during treatment with etanercept, alone or combined with methotrexate. Reproduced with permission from Gottlieb et al. [57]. © 2012 The Authors. BJD © 2012 British Association of Dermatologists



group and in 24 % of patients receiving methotrexate alone. The most common treatment-related adverse events were increased levels of hepatic enzymes.

Randomized trials investigating the combination of adalimumab and methotrexate are lacking in psoriasis, although positive results have been reported among patients with rheumatoid arthritis [59, 60]. The findings of the aforementioned randomized trials are further supported by numerous uncontrolled studies and case series that have shown beneficial effects of combinations of biologic therapies with methotrexate in patients with psoriasis or psoriatic arthritis [45, 61–76]. These studies have provided useful insights into the effectiveness and tolerability of combination therapy in routine clinical practice.

Wee et al. [72] retrospectively investigated the safety of infliximab infusions in 59 patients with psoriasis who received infliximab over a 9-year period at a single center in the UK. In this study, 56 % of patients were receiving concomitant systemic therapies; 41 % were receiving methotrexate [72]. Overall, acute infusion reactions were associated with 10 of 858 infliximab infusions (1.2 %), of which three (0.3 %) were severe. The incidence of infusion reactions was significantly lower in patients receiving infliximab with methotrexate than in those receiving infliximab alone (4 versus 27 %, respectively; $P = 0.05$), potentially as a result of decreased formation of anti-infliximab antibodies due to methotrexate. Another recent study ($n = 45$) investigated the effectiveness of combination therapy with methotrexate and adalimumab (11 treatment episodes) or adalimumab dose escalation (i.e., weekly dosing; 32 treatment episodes) in patients with psoriasis (a subset of approximately 25 % also had psoriatic arthritis) [74]. Patients were included in this study if they had an inadequate response, determined by the physician's discretion, to standard adalimumab dosing. Combination therapy resulted in PASI 50 response rates of 9 % after 12 weeks and 18 % after 24 weeks; the corresponding values in patients with increased adalimumab doses were 25 and 35 %, respectively. The mean weekly dose of methotrexate used in this study was 9.5 mg per treatment episode. Adverse event rates were not reported in this trial; no serious adverse events were judged by the investigators to be related to the study medication. The study was too small to draw definitive conclusions but suggests that, at least for some patients, adalimumab dose escalation may be more beneficial than adding methotrexate.

3.2 Combinations Involving Cyclosporine

Cyclosporine therapy allows for regulation of the immune system through a different mechanism of action than current biologic agents, and their combination may improve control of lesion formation. The efficacy of therapy with

cyclosporine and adalimumab was investigated in a non-randomized, open-label study in patients with active psoriatic arthritis that was refractory to methotrexate treatment [77]. After 12 months, PASI 50 response criteria were met by 95 % of patients receiving combination therapy, compared with 85 % of patients receiving adalimumab alone and 65 % of those receiving cyclosporine alone ($P = 0.003$ versus combination treatment). In a small-scale, open-label study of patients with refractory psoriasis ($n = 7$), combination therapy with etanercept and low-dose cyclosporine (200 mg/day initially, then 100 mg/day) resulted in a mean reduction in PASI scores of 93.2 % at the end of the maintenance treatment period [78]. In addition, combinations of cyclosporine with biologic therapies have also been studied in a number of nonrandomized trials and case reports [45, 65–67, 79–82]. More rigorous studies are required to validate the safety and efficacy of these treatment regimens. Care must be taken when prescribing cyclosporine, because of concerns about nephrotoxicity, hypertension, and numerous drug interactions. Patients receiving cyclosporine in combination with other agents that suppress the immune system, such as TNF- α inhibitors, should be closely monitored for development of infections. Additionally, cyclosporine is not an option for long-term treatment of psoriasis, because of cumulative toxicity concerns.

3.3 Combinations Involving Retinoids

Individuals with psoriasis, many of whom have had significant phototherapy or excessive sun exposure, are at an increased risk of nonmelanoma skin cancers, such as squamous cell carcinoma and basal cell carcinoma [83]. To help reduce the risk of these types of cancer, oral retinoids may be given in combination with other systemic therapies. This method of treatment decreases the incidence of actinic keratosis and squamous cell carcinoma [31, 45, 84] but may also improve the underlying psoriasis. In a randomized, controlled, investigator-blinded pilot study, 60 patients with moderate-to-severe chronic plaque psoriasis were randomized to receive acitretin (0.4 mg/kg daily), etanercept (25 mg twice weekly), or the two agents in combination with reduced etanercept dosing (25 mg etanercept once weekly plus acitretin 0.4 mg/kg daily) [53]. At 24 weeks, a PASI 75 response was achieved in 30 % of patients receiving acitretin alone, compared with 45 % of those receiving etanercept alone and 44 % of those receiving combination therapy ($P = 0.001$ for both etanercept groups versus acitretin; Fig. 2) [53]. All treatments were well tolerated, and the only reported adverse event was mild mucosal dryness in two patients in the acitretin group and one patient in the combined group. No malignancies were reported.

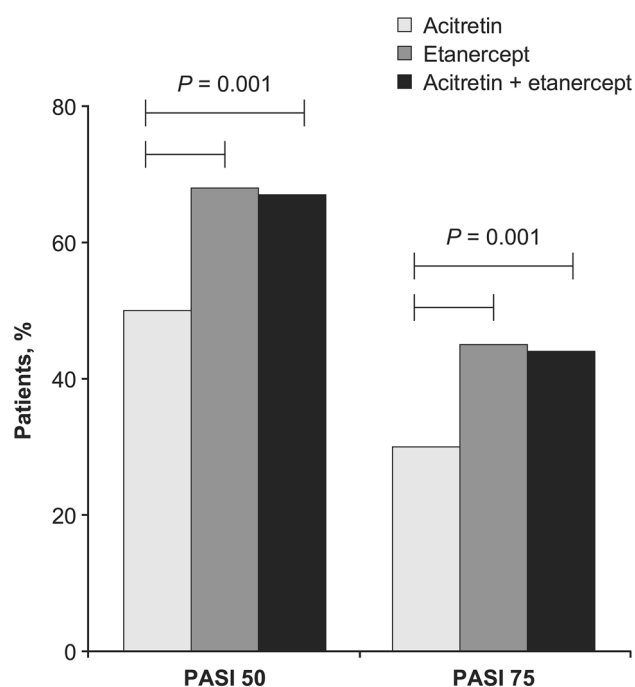


Fig. 2 Psoriasis Area Severity Index of ≥ 50 % (PASI 50) and ≥ 75 % (PASI 75) response rates at 24 weeks in patients with active plaque psoriasis treated with acitretin, etanercept twice weekly, or the two agents in combination with reduced use of etanercept (etanercept once weekly plus daily acitretin) [53]

Efficacious treatment of psoriasis using combinations of biologic therapies with retinoids has also been reported in a number of uncontrolled studies and case reports [45, 64, 66, 67, 85–90].

3.4 Phototherapy–Drug Combinations

Although phototherapy is not a pharmacologic intervention, it is an important treatment modality in the management of psoriasis. The combination of etanercept and narrow-band ultraviolet B (NB-UVB) or etanercept alone were studied in a trial of 75 patients with moderate-to-severe psoriasis that had not reached PASI 90 after 12 weeks of etanercept monotherapy [91]. The investigators observed that there were significant challenges to NB-UVB therapy adherence, with only 21.6 % of patients receiving ≥ 80 % of NB-UVB treatments. After 24 weeks, there was no significant difference in PASI 75 response rates between patients receiving etanercept monotherapy and those receiving the combination of etanercept and NB-UVB. However, in a small subset of patients with high adherence to NB-UVB therapy, PASI 75 response rates were found to be significantly improved as compared with patients receiving etanercept alone. Poor adherence to NB-UVB therapy was also observed by Park et al. [92] in an etanercept combination trial of obese patients with psoriasis. Interestingly, the combination of etanercept and

NB-UVB did not lead to greater clearance of psoriasis than etanercept alone in these patients, and the investigators speculated that the poor adherence to NB-UVB therapy may have been due to patient satisfaction with the degree of psoriasis improvement from etanercept monotherapy. As with the other combination modalities, a number of uncontrolled clinical trials have shown positive results when NB-UVB therapy was combined with etanercept, adalimumab, and ustekinumab [93–99]. Thus, combinations of biologics and phototherapy may increase efficacy but are limited by adherence to therapy and concerns regarding the potential for skin cancer formation.

3.5 Combinations Involving Biologics

The combination of biologic agents has not been studied thoroughly in clinical trials, because of the relatively recent adoption of their use and concerns over blocking two pathways of the immune system. Thus, there are limited data available on the efficacy and safety of this type of therapy. A single case report has described successful treatment of psoriasis with adalimumab and ustekinumab in a patient who had not responded to combination therapy with methotrexate and ustekinumab [45]. However, the combination of biologic therapies did not improve this patient's psoriatic arthritis. Physicians should proceed cautiously when considering the use of combinations of biologic agents; experience with this approach is very limited at this time and may have unknown consequences.

4 Clinical Implications and Unanswered Questions

Although the studies reviewed above have provided some evidence that therapies combining a conventional agent with a biologic are more effective than those agents used alone, and may be well tolerated in patients with psoriasis, there are still a number of questions that remain regarding the most appropriate use of this strategy [31]. Some of the trials involved patients with psoriatic arthritis and included those with psoriasis disease severity below the criteria for psoriasis trials, or had small sample sizes, or measured efficacy using inadequate or low efficacy endpoints (e.g., PASI 50). It is necessary to identify the safest and most effective combinations to limit potentially dangerous adverse events while achieving higher rates of skin clearance. In addition, the long-term safety of combination therapy is of particular concern; data are not available from controlled trials. Combination therapy with biologics may be beneficial in the management of comorbidities commonly found in patients with psoriasis. For instance, both TNF- α inhibitors and methotrexate reduce the risk of

cardiovascular events, but it is unknown if their combination would produce additional benefits [44]. To fully understand the potential positive or negative influence of combination therapy on comorbidities, additional studies are required. Patients with psoriasis are also more likely to develop other health issues such as metabolic syndrome, which may be affected by combination therapy. TNF- α inhibitors may improve insulin resistance and fasting glucose levels, suggesting a possible beneficial role in managing metabolic syndrome, but other studies have reported increases in total cholesterol and high-density lipoprotein cholesterol following treatment [44]. Likewise, further studies are needed to elucidate the effect of combination therapy on metabolic syndrome. Combination therapy may be a more cost-effective method of managing psoriasis, but economic evaluations are needed to determine potential savings in healthcare costs. Disease management for patients with severe psoriasis could be improved, particularly if the findings to date with short-term use of phototherapy or traditional systemic agents in combination with biologic therapy are confirmed in the long term. Finally, it remains to be determined if biologic therapies can be used in combination without an increased safety risk.

5 Emerging Biologics

A number of new biologic therapies are currently in development for the treatment of psoriasis (Table 4) [100–103], including those that target IL-17A or its receptor, IL-23, and T cells [21]. It is not yet known how these therapies, many of which are in phase III clinical trials, will fit into the psoriasis treatment paradigm. These agents offer the potential for selective targeting of key processes in the pathogenesis of psoriasis. For example, compared with TNF- α , IL-17A is a cytokine that is downstream in the psoriasis pathogenesis pathway. As such, inhibiting this cytokine or its receptor may theoretically block psoriatic

plaque formation without disrupting upstream cytokines that may be involved in other processes. Downstream blockade therefore has the potential to lessen the unwanted off-target effects associated with more upstream blockade. This selective targeting may also translate into a high level of efficacy, potentially reducing the need for combination therapy and offering patients a more convenient method to meet their treatment goals.

6 Conclusions

There is evidence demonstrating that combination therapy with biologic agents and conventional systemic therapies or phototherapy is effective and well tolerated in the management of moderate-to-severe psoriasis, although there are several limitations with respect to existing data (e.g., many psoriatic arthritis trials; patients often had less severe psoriasis; small studies; assessment of PASI 50 and not PASI 75 as the primary efficacy measure). Combination therapy offers the potential for improved treatment of patient subgroups in which currently available therapies may be of only limited benefit, such as patients with joint involvement or those at risk of end-organ toxicity with methotrexate, or for whom monotherapy has not yielded a desired benefit. Although combination therapy may improve treatment outcomes compared with individual monotherapy, the efficacy benefit from combination treatment can still remain below the desired target. The potential importance of higher treatment goals being achieved by monotherapy is highlighted by the emergence of new biologic therapies, such as IL-17A inhibitors. These agents selectively target key processes in the pathogenesis of psoriasis and thus may offer better efficacy than current biologic and systemic therapies. Therefore, these agents may allow more patients and prescribers to meet their psoriasis management goals without the need to augment treatment regimens with additional agents.

Table 4 Biologic therapies currently under development for the treatment of psoriasis [100–103]

Agent	Description	Mechanism of action	Current status
Secukinumab	Fully human monoclonal antibody directed against IL-17A	Blockade of IL-17A action	In phase III clinical trials
Brodalumab	Monoclonal antibody directed against IL-17 receptor	Blockade of IL-17A action	In phase III clinical trials
Ixekizumab	Monoclonal antibody directed against IL-17	Blockade of IL-17A action	In phase III clinical trials
Guselkumab (CNTO1959)	Fully human HuCAL-based antibody directed against the p19 subunit of IL-23	Blockade of IL-23 action	In phase II clinical trials
MK-3222/SCH-900222	Humanized monoclonal antibody directed against the p19 subunit of IL-23	Blockade of IL-23 action	In phase III clinical trials
Tregalizumab (BT-061)	Monoclonal antibody directed against CD4 cells	Activation of regulatory T cells	In phase II clinical trials

HuCAL human combinatorial antibody library, *IL* interleukin

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Conflict of Interest Dr. Cather has served as a speaker or consultant for AbbVie, Janssen, Leo, and Novartis. She has served as an investigator in clinical trials for Amgen, Celgene, Galderma, Lilly, Merck, Novartis, Pfizer, and Tolmar. She owns no stock and has no ownership interest in any pharmaceutical company.

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